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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,358	ADAMS ET AL.	
	Examiner	Art Unit	
	Sally A. Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,35,38,39,41-44,46,48,49 and 51-73* is/are pending in the application.

4a) Of the above claim(s) *56,58-61,64 and 66-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,35,38,39,41-44,46,48,49,51-55,63,65 and 71-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/6/2004 and 5/24*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 5/24/2005. Claims 32, 35, 41, 43, 44, 57, and 71-73 have been amended, claims 1-31, 33-34, 36-37, 40, 45, 47, and 50 have been canceled, and no claims have been added. Claims 32,35,38,39,41-44,46,48,49 and 51-73 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 12/6/2004 and 5/24/2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 32, 35, 38, 39, 41-44, 46, 48-49, and 51-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are broadly drawn to methods of detecting a variant CGI-69 polynucleotide comprising detecting a polynucleotide encoding a polypeptide comprising an amino acid sequence having at least 98% sequence identity to the amino acid of SEQ ID NO:3, the long version of CGI-69 encoded by the polynucleotide of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention of these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 32, 35, 38, 39, 41-44, 46, 48-49, and 51-73 are broadly drawn to methods of detecting a variant CGI-69 polynucleotide under the pretense that these sequences and their detection is in some way is correlated with metabolic diseases as the sequence shares similarity to the mouse ortholog that was found to be up regulated 2-fold in brown adipose tissue of mice exposed to cold for 48hr. However, as will be further discussed, there is no support in the specification and prior art for the implementation of the presently claimed methods with respect to these sequences. The invention is in a class of invention which the CAFC has characterized as

"the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The specification teaches that the "analysis of BAT genes upregulated by cold identified a 348 bp gene fragment whose QEA profile indicated significant induction in cold-challenged mice"(Pg. 83). Using a murine EST database, a putative murine full-length gene encoding a protein with high homology to the human putative protein CGI-69 was found(86% identical/98% similar). Following an inquiry into the domains/motifs had by CGI-69 and the mitochondrial localization, the specification teaches of subsequent studies on the assumption that human variants of CGI-69 have a stake in affecting the mitochondrial membrane potential($\Delta\Psi m$). The specification recites on page 85 that "a variety of CGI-69 clones were isolated from human liver upon PCR amplification and cloning, one of which corresponded to the original AF151827 sequence in GenBank", and other versions including the "CGI-69L"(W64L). The specification continues to teach that "in humans, both the short form(s) and long form(s) of the gene were expressed at various ratios" with transcripts for CGI-69 being widely-detected in human tissues, with "particularly high expression in testis and kidney"(Pg. 85). The specification further teaches that only the over-expression of a CGI-69 fusion protein having a carboxy FLAG-tagged CGI-69 showed diminished $\Delta\Psi m$. The specification teaches that similar untagged CGI-69, amino-FLAG-tagged CGI-69, and even over expression of human CGI-69 had no effect on $\Delta\Psi m$. There is no evidence that any correlation exists between metabolic disorders or uncouplers and the detection of any of the claimed sequences, variants or wild-type.

The prior art is silent with regard to the detection of human CGI-69 and a correlation to metabolic disorders. However, there is a large body of knowledge in the prior art related to uncoupling protein(UCPs) homologs in general, and their tenuous relationship to metabolic

diseases or disease states. The art is highly unpredictable with regard to the functionality of a homolog of a gene described in rodents and mice brown adipose tissue(BAT) as an UCP. Adams teaches the unpredictability of extrapolating this data from other species such as rodent or mouse. The reference teaches that, "UCP2" is an interesting candidate for involvement with thermogenesis. However, expression data yield conflicting evidence for the role of UCP2 in situ"(Adams Pg.712). The reference teaches that while UCP2 expression is induced in a leptin deficient mouse(ob/ob) and leptin administration to these ob/ob mice was able to normalize liver proton leak, "but unfortunately leptin-induced changes in hepatocyte UCP2 expression were not present"(Adams, 712). The reference teaches that a homolog to an originally isolated, over-expressed UCP, does not always retain its function in a different system. The art further teaches that another homolog, to UCP2, has produced "numerous data which raise the question whether UCP2 acts as an uncoupler in situ. Lastly, Adams teaches that with respect to another UCP, that "studies correlating UCP3 expression with metabolic status do not yield compelling evidence to confirm an important contribution of this homolog's activity toward driving metabolic rate in vivo". The reference concluded by admitting that, most analyses of putative UCP homologs rely on indirect indices of function, and challenges remain to optimize such assessments further"(Adams 713). Thus, even for the extrapolation of a homolog or ortholog's function from one system to another, in addition to the detection of a correlation to a metabolic disorder, it is highly unpredictable as to whether a particular sequence will be disease associated. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is a significant number of parameters which would have to be studied to apply this technology to an, as of yet knowledge in the art lacks teachings of the detection of the claimed sequences and a correlation

to metabolic diseases. The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention, one would have to establish a relationship between the variant of CGI-69 and some physiological or disease state. Indeed, even to use the method of claim 32 to detect a disease associated with a sample nucleic acid, one would need to know that the variant sequence in CGI-69, was in some way associated with the underlying biochemical process leading to a specific disease. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method of screening for a mutation or a variant sequence would be useful in disease detection, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between any sequence variant and any disease or condition. The practice of the method as currently claimed, would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Working Examples

The specification has no working examples of the detection of any variant sequence in humans that is associated with any metabolic disease. The specification teaches that only the

over-expression of a CGI-69 fusion protein having a carboxy FLAG-tagged CGI-69 showed diminished $\Delta\Psi m$. The specification teaches that similar untagged CGI-69, amino-FLAG-tagged CGI-69, and even over expression of human CGI-69 had no effect on $\Delta\Psi m$.

Guidance in the Specification.

The amount of direction or guidance presented in the specification with regard to how to use the instant invention is minimal. With regard to claims directed towards the detection of variant polynucleotides in CGI-69, applicant speculates that detection of variants will aid in the discovery of genes whose sequences "lead to biological changes that predispose to metabolic disease, or are in fact predictive of the progression of disease"(specification, page 2). However, since the effects of any given mutation or other variant on gene activity are highly unpredictable, it is impossible to predict from the teachings of the instant specification what identifications can be made using the instantly claimed screening method for nucleic acids. That is, the specification does not provide any guidance as to how another variant as compared to the splice variant of SEQ ID NO:1 and the other version SEQ ID NO: 2 would be associated with any method of detecting, i.e., what detecting a variant would be detecting. The specification does not discuss whether this particular, detected variant will increase the likelihood of a positive or negative response to any drug. The specification provides no guidance or working examples that teach or demonstrate the ability to use the disclosed method of detecting sequences as markers for any disease in particular, or for disease in general.

Level of Skill in the Art

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed a number of different "wild-type" or reference variant sequences, it remains highly unpredictable as to the biological significance of detecting any of these sequences. Thus, the practice of this method of detection for the use in their characteristic correlation seen in metabolic disorders requires the knowledge of unpredictable and potentially non-existent associations between the instantly elected method of detecting and some phenotypic trait. Even if the prophesized, detected variant sequences are in some way associated with some metabolic disease, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the particular sequence is associated. That is, it is unpredictable as to whether the presence of a particular allele, splice variant, truncation, present in variant forms of CGI-69 would confer a higher or lower likelihood of having/detecting/treating/preventing a particular disease. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to detect a construct consisting of a carboxy-FLAG tagged CGI-69 fusion protein whose over expression results in a decreased $\Delta\Psi m$, and a possible relevance to a metabolic disease.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the correlation of a DNA sequence to a metabolic disease depends upon numerous known and unknown parameters such as the specific system in which the DNA is acting, potential epigenetic interactions of charged molecules, and stearic hindrances, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides

insufficient guidance to overcome the art recognized problems in the use of the method as claimed for the CGI-69 sequences. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

Applicant's arguments with respect to claims 32, 35, 36, and 38-53 have been fully considered but are not persuasive. Applicants argue that "one skilled in the art would have been able to use the claimed methods to identify variant CGI-69 polynucleotides from a biological sample without undue experimentation" and is as such sufficient to meet the enablement requirement. Applicants next restate their data with respect to the 86% identity shared between the human CGI-69 and that of the mouse and shared structural similarities, motifs and conclude that "one skilled in the art would have expected CGI-69 to be a mitochondrial carrier protein"(Pg. 9). However, it is again asserted by the office that when tested, none of SEQ ID NOS:1-4 proved to function as a mitochondrial carrier protein, only the over-expression of carboxy-FLAG-tagged CGI-69 diminished $\Delta\Psi m$, similar to a human uncoupler(UCP3)(Specification page 86). As a result, no claimed variant was shown to function in any particular capacity in the cellular respiration.

35 U.S.C. 112, Written Description Rejection

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 32, 35, 38, 39, 41-44, 46, 48-49, and 51-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses SEQ ID NO: 1 which corresponds to the full length cDNA of the long version of human CGI-69 polynucleotide. SEQ ID NO: 2 which corresponds to the full length wild-type human CGI-69 polynucleotide. SEQ ID NOS: 3 and 4 correspond to the polypeptides encoded by SEQ ID NOS 1 and 2 respectively. Claims 32, 35, 38, 39, 41-44, 46, 48-49, and 51-73 are directed to encompass sequences comprising undefined, variants of CGI-69 "comprising detecting polynucleotides encoding a polypeptide comprising an amino acid sequence having at least 98% sequence identity to SEQ ID NO:3" and further to nucleic acid probes that hybridize to a polynucleotide encoding a polypeptide comprising an amino acid sequence having at least 98% sequence identity to SEQ ID NO:3 under stringent conditions". A review of the full content of the specification indicates that the sequence of nucleotides of SEQ ID NOs: 1-4 and all aforementioned variations are essential to the operation and function of the claimed invention. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NOs:1-4, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The named ORF is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for isolating and characterizing cDNA sequences from *E. grandis*, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe *E. grandis* cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the specification does, does not necessarily describe the cDNA itself. No sequence

information indicating which nucleotides constitute *E. grandis* cDNA appears in the application. Accordingly, the specification does not provide a written description of the invention of claims 1, 4, and 6-15.

Therefore, none of the sequences encompassed by the claim meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant and undefined. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Response to Arguments

Applicant's arguments with respect to claims 32, 35, 36, and 38-53 have been fully considered but are not persuasive. Applicants assert that the specification has provides written description to the claimed invention by referencing several parts of their specification e.g. pages 84 and 85 on page 10 of the response. However, the large genus of sequences encompassed by the many undefined variants comprising at least 98% sequence identity with SEQ ID NO:3, already a variant of CGI-69, is not deemed to be adequately described in the present specification.

New Matter

3. Claim 65, is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "nucleotides 265 to 288 of SEQ ID NO:1" in claim 65 appears to represent new matter. No specific basis for this limitation was

identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. Since no basis has been identified, the claims are rejected as incorporating new matter.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A. Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris
8/3/2005

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600